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(72) Inventors: KRIEG, Arthur, M.; University of Iowa, Dept. of Internal Medicine, 540 EM RB, Iowa City, IA 52242 (US). WEINER, George; University of Iowa, Dept. of Internal Medicine, 540 EM RB, Iowa City, IA 52242 (US).		(88) Date of publication of the international search report: 13 January 2000 (13.01.00)																																																								
(74) Agent: LOCKHART, Helen, C.; Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210 (US).																																																										
(54) Title: METHODS AND PRODUCTS FOR STIMULATING THE IMMUNE SYSTEM USING IMMUNOTHERAPEUTIC OLIGONUCLEOTIDES AND CYTOKINES																																																										
(57) Abstract																																																										
<p>The present invention relates to synergistic combinations of immunostimulatory CpG oligonucleotides and immunopotentiating cytokines. In particular, the invention relates to methods of stimulating an immune response using the synergistic combination of compounds and products related thereto.</p>																																																										
<p>The graph shows the survival of mice over 60 days post-tumor inoculation. The 'NO IMMUNIZATION' group shows the lowest survival, dropping to 0% by day 40. The 'CpG ODN' group shows improved survival, reaching 0% by day 50. The 'Id/GM-CSF' group shows the highest survival, with approximately 30% of mice surviving at day 60. The 'Id/GM-CSF + CpG ODN' group shows the best survival outcome, with approximately 70% of mice surviving at day 60.</p> <table border="1"> <caption>Approximate Survival Data from Graph</caption> <thead> <tr> <th>Days Post Tumor Inoculation</th> <th>NO IMMUNIZATION (%)</th> <th>CpG ODN (%)</th> <th>Id/GM-CSF (%)</th> <th>Id/GM-CSF + CpG ODN (%)</th> </tr> </thead> <tbody> <tr><td>0</td><td>100</td><td>100</td><td>100</td><td>100</td></tr> <tr><td>10</td><td>100</td><td>100</td><td>100</td><td>100</td></tr> <tr><td>20</td><td>100</td><td>100</td><td>100</td><td>100</td></tr> <tr><td>25</td><td>10</td><td>80</td><td>100</td><td>100</td></tr> <tr><td>30</td><td>0</td><td>40</td><td>80</td><td>90</td></tr> <tr><td>35</td><td>0</td><td>20</td><td>60</td><td>85</td></tr> <tr><td>40</td><td>0</td><td>10</td><td>40</td><td>70</td></tr> <tr><td>45</td><td>0</td><td>5</td><td>30</td><td>70</td></tr> <tr><td>50</td><td>0</td><td>0</td><td>30</td><td>70</td></tr> <tr><td>60</td><td>0</td><td>0</td><td>30</td><td>70</td></tr> </tbody> </table>				Days Post Tumor Inoculation	NO IMMUNIZATION (%)	CpG ODN (%)	Id/GM-CSF (%)	Id/GM-CSF + CpG ODN (%)	0	100	100	100	100	10	100	100	100	100	20	100	100	100	100	25	10	80	100	100	30	0	40	80	90	35	0	20	60	85	40	0	10	40	70	45	0	5	30	70	50	0	0	30	70	60	0	0	30	70
Days Post Tumor Inoculation	NO IMMUNIZATION (%)	CpG ODN (%)	Id/GM-CSF (%)	Id/GM-CSF + CpG ODN (%)																																																						
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INTERNATIONAL SEARCH REPORT

Inte. onal Application No

PCT/US 99/07335

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K38/19 A61K31/70 //(A61K38/19,31:70)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WEINER G J ET AL: "Immunostimulatory oligodeoxynucleotides containing the CpG motif are effective as immune adjuvants in tumor antigen immunization." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 SEP 30) 94 (20) 10833-7. , XP002120387 cited in the application page 10833 page 10836 ----- -/-	1-20

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search

27 October 1999

Date of mailing of the international search report

25. 11. 99

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/07335

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>CHU R S ET AL: "CpG oligodeoxynucleotides act as adjuvants that switch on T helper 1 (Th1 immunity." JOURNAL OF EXPERIMENTAL MEDICINE, (1997 NOV 17) 186 (10) 1623-31. , XP002910130 page 1623 -page 1624, left-hand column page 1629</p>	1-20
A	<p>DAVIS H L ET AL: "CpG DNA is a potent enhancer of specific immunity in mice immunized with recombinant hepatitis B surface antigen 'published erratum appears in J Immunol 1999 Mar 1;162(5):3103!." JOURNAL OF IMMUNOLOGY, (1998 JAN 15) 160 (2) 870-6. , XP002109526 page 870 page 874 -page 875</p>	1-20
P,X	<p>LIU H M ET AL: "Immunostimulatory CpG oligodeoxynucleotides enhance the immune response t vaccine strategies involving granulocyte-macrophage colony-stimulating factor." BLOOD, (1998 NOV 15) 92 (10) 3730-6. , XP002120388 the whole document</p>	1-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/07335

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-10, 14-16 (part) and 17-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
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because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
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Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
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- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.